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Hepatomegaly in Neuroblastoma Stage 4s: Criteria for Treatment of the Vulnerable Neonate

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Infants with neuroblastoma (NBL) frequently present as stage 4s and overall, such patients have a good prognosis. However, not all survive, and neonates with hepatomegaly are particularly at risk. We therefore reviewed our 4s experience, the objective being to identify lethal patterns of disease progression.

The specific aims of this work were (1) to develop a semiquantitative scoring system based on the severity of signs and symptoms that alone or in combination presaged a fatal outcome, and (2) to determine if early intervention could reverse life-threatening disease.

Thirty-five patients were seen over a period of 50 years. The signs and symptoms of organ distress caused by hepatomegaly occurred in the lungs, kidneys, gastrointestinal tract (GI), the inferior vena cava (IVC), and the liver. A scoring scale reflecting organ compromise was developed, the scores ranging from 0 (0 compromise) to 10 (all 5 systems showing evidence of impairment). Scores were derived for 32 of 35 patients; 13 were 4 weeks old or under (neonates) when first seen, and 19 were aged 1–12 months (infants). Neonates were more likely than infants to develop increasing symptomatology (50% versus 25%) and were more likely to die when a score of 2 or more developed. None of the 6 neonates who did so survived despite treatment, compared with three of four infants.

Early intervention is recommended: (1) for 4s neonates who develop a score of 1 and (2) for older infants with a score ≥2.

Key words: neonatal 4s, neuroblastoma, treatment

INTRODUCTION

Babies with neuroblastoma (NBL) frequently present as stage 4s under the International Staging System (INSS) [1], having a primary tumor that does not cross the midline, and distant disease confined to the liver, skin, or marrow, without bone metastases. Despite this large and widespread tumor burden, however, 4s disease carries a good prognosis, along with the expectation of spontaneous regression. The potential benefits of early intervention, therefore, need to be weighed against the potential adverse early and late effects of anti-neoplastic therapy, including acute toxicities, later disturbances of growth, and the risk of oncogenesis [2]. These considerations have led us and others to a policy of minimizing treatment in NBL 4s [3]. However, it is well-known that not all such patients survive, and that neonates, i.e., babies less than 4 weeks old, are particularly at risk because of functional impairments caused by hepatomegaly [4–6].

We recently cared for a neonate diagnosed with NBL 4s who had an enlarged liver and died despite treatment after progressive physiological compromise had become manifest. This case prompted a more detailed review of our institutional experience with such patients. The objective was to define criteria that would identify patients at risk of lethal complications from hepatomegaly who might still be amenable to early intervention and for whom spontaneous regression should not be awaited. Additional problems secondary to liver enlargement could develop and become irreversible during the interval. The specific aim was to develop a scoring system, based on these criteria, which could be used to trigger therapy in vulnerable patients.

CASE PRESENTATION

TB was a 3,544 g full-term birth after an uncomplicated pregnancy. The Apgar scores were $8^{1}9^{5}$. Hepatomegaly was noted on initial newborn examination at 8 cm below the right costal margin, plus a left abdominal mass. Ultrasound examination confirmed the mass as left suprarenal, with no calcifications. He was transferred to The Children's Hospital of Philadelphia (CHOP) in good condition for further evaluation (Table I).

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TABLE I. Case Report: Progression of Hepatomegaly and Abdominal Girth*

Day	Liver edge (cm below costal margin) Right	Left	Abdominal girth (cm) Maximum	Increment (avg. cm/day)
1 Birth				
2	8	4	35	
4			37	1
5	9.5	7	40.5	3.5
7	12	8	41	0.25
12	12	9	42	0.5
13 Discharge			42.5	0.5
17	14	10	44	0.33
19 Readmission				
20 CT	14.5	10.5	45.5	0.5
22	13.5	12	47.5	1
23 Radiation			48	0.5
24 Silastic patch, death				

*The rapid enlargement of the liver due to NBL involvement could be assessed by either the span of the liver palpable below the costal margins, or by the abdominal girth. Girth became a better index as the liver edge approached the pelvic brim.

He was alert and vigorous, breathing comfortably. The heart and respiration rates, respectively, were 153 and 60. The abdomen was rounded with a firm liver palpable in both upper quadrants and extending just below the umbilicus into the right lower quadrant. There was no distension of the abdominal veins, no pedal edema, and no skin lesions were noted. Tabulated laboratory data follow:

Urine VMA spot:	positive
VMA (quant):	475.9 mg/g creatine (upper normal for age 16.0)
HVA (quant):	386.2 mg/g creatine (upper normal for age 29.8)
Chest X-ray film:	no abnormalities
Skeletal survey:	no metastases, incidental fracture of the left clavicle
Bone scan:	negative
Abdominal sonogram:	L adrenal mass 5 × 5 × 6 cm liver heterogeneous enlargement, but no focal lesions
Bone marrow biopsy:	rare NBL clumps
Ferritin:	231 ng/ml (upper limit of normal for neonates = 500 ng/ml)
LDH:	1,391 U/L: (normal range 934–2,150 for neonates)

He was diagnosed with NBL stage 4s on the basis of clinical findings, increased catecholamines, and tumor in the marrow. Neither the liver nor the suprarenal tumor were biopsied.

Since he was asymptomatic, he was managed expectantly at first, but the abdominal girth continued to increase at approximately 1 cm per day, attaining 45.5 cm at 20 days of age. He became irritable and started to vomit, so it was decided that treatment should be instituted. Irradiation therapy (RT) and chemotherapy (CT) were considered and it was elected to give CT initially.

On readmission, he was tachypneic and irritable. Abdominal wall veins were distended, and there was edema of the lower abdomen, scrotum, and lower extremities. The firm liver was palpable in all quadrants. Cisplatin and etoposide were given in half-doses, based on body weight. He became more edematous over the three days after initiating CT, and was more irritable, not feeding well, and oligouric. Although his renal problems could be due in part to the cisplatin, it was felt more likely to be poor perfusion from compression by the liver on the inferior vena cava (IVC) and renal vessels. He was found to have a blood glucose of 38 mg/dl. His extremities and abdomen (girth now 48 cm) were cyanotic and poorly perfused, despite the addition of supplemental oxygen, mechanical ventilation, and vigorous fluid resuscitation. Chest roentgenogram showed extremely small lung volumes with the increasing size of the liver. Neutropenia, anemia, and coagulopathy were noted. An abdominal ultrasound demonstrated hepatic compression of the IVC with poor return of blood to the right heart. Despite increased ventilatory settings and hemodialysis, he developed a mixed respiratory and metabolic acidosis. Emergent RT to his abdomen (300 cGy) later that day produced no improvement. His abdominal girth did not decrease, and he became anuric.

Surgical decompression by creation of a ventral hernia with a Silastic patch on the next day produced transient improvement: his lower body became pink and well-perfused immediately after the abdominal wall was opened. However, his increasing ventilatory requirements led to bilateral pneumothorax soon after surgery. Even

after relief of pneumothorax by placement of chest tubes, the lower body again was cyanotic and poorly perfused. He remained anuric and edematous, with continued clinical deterioration unresponsive to pressors and fluids. He was pronounced dead later in the day, at 24 days of age.

Autopsy Findings

IVC compression by the caudate lobe of the liver was found and widely disseminated tumor. Analysis of the tumor showed a low mitosis karyorrhexis index, triploidy, and no N-*myc* amplification.

RETROSPECTIVE REVIEW METHODS

Patients with 4s disease who received care at our hospital (CHOP) during the interval 1970 to 1994 were identified by the Cancer Center Tumor Registry, the Pathology Department records of autopsies and surgical pathology specimens, and a previous review of such cases from 1944 to 1977 from this institution [7]. A total of 41 patients were identified and reviewed.

Exclusion Criteria

Four children are not included for the following reasons: treatment given elsewhere, retrospective change of stage from 4s to 4, change of diagnosis from NBL to peripheral neuroectodermal tumor, and age 5 years at diagnosis no longer fitting the INSS 4s definition. Two additional patients were excluded because they never had liver disease and the focus of this review is on the complications of hepatomegaly. There remained 35 patients of whom 13 were neonates.

Existing in-patient records, Ambulatory Oncology Clinic records, Tumor Registry files, autopsy reports, and surgical pathology reports were reviewed. In the chart reviews, we noted any mention of signs and symptoms of physiologic compromise by hepatomegaly. Three pre-1970 records were not detailed enough to score, and are therefore not included in those analyses.

Comparison Groups

The babies were divided into two age groups: neonates (<4 weeks of age) and infants (1 to 12 months old). Neonates with NBL of other stages (1 to 4), but not 4s, were identified by a review of the same resources. Four cases of incidental findings of NBL stage 1 at autopsy, when death was clearly due to other causes, were excluded. One patient who died of progressive tumor was excluded because of uncertainty about the diagnosis: NBL versus peripheral neuroectodermal tumor.

Two comparisons were made: first, neonates with 4s versus infants with 4s NBL; and second, 4s versus non-4s neonates.

EXTENT OF DISEASE

Neonates

All 13 4s neonates had liver involvement; in two it was discovered at laparotomy, and hepatomegaly developed subsequently. One patient also had both skin nodules and rare tumor cell clumps in the marrow. Three of the 13 had skin lesions without marrow disease, and three had marrow involvement without skin lesions. Some of the 13 babies included in these analyses had additional sites of NBL that lie outside the official 4s definition. They were: pleura, pancreas, peritoneum, and abdominal wall. These findings gave rise to the expanded concept of 4s disease as reported by Evans et al [7] in 1980.

Infants

All but one of the 22 infants presented with hepatomegaly; the one patient had a skin lesion initially and hepatomegaly developed over the next 3 months. Eight patients had rare tumor clumps in the marrow, four had skin lesions, 1 had skin and marrow involvement, seven patients had no distant lesions, and data were not available on two patients.

Criteria for Assessing Symptomatic Hepatomegaly

Common signs and symptoms of physiologic compromise from abdominal NBL emerged from examination of these cases from our institution and from the literature. Hepatomegaly from tumor involvement can cause mechanical compromise of respiratory, cardiovascular, gastrointestinal (GI), and renal function [8–10]. It is also associated with disseminated intravascular coagulation (DIC). Diffuse hepatic involvement rarely leads to hepatic failure

Physiologic compromise of the GI, respiratory, vascular, renal and hepatic organ systems was scored as none, mild, or severe/life-threatening dysfunction. Using this schema, symptoms of 32 of the 35 patients were assessed: (1) at presentation, (2) at the time of maximum symptoms, and (3) at the time of decision to treat. The three patients with records not detailed enough for assessment of symptomatology are included only in the survival data. A numerical scoring of signs and symptoms in each system according to their severity was developed and is presented in Table II.

RESULTS

Extent of Compromise and Outcome

The amount of compromise at various points of clinical evolution is shown in Table III. The infants were divided according to age, i.e., neonate versus 1 to 12 months old. At diagnosis, the degree of physiologic compromise was not greatly different, 9 of 13 (69%) neonates scored zero

TABLE II. Functional Compromise Due to Levels of Hepatomegaly

		Score
GI		
Emesis of >10% of intake	mild	1
Repeated emesis requiring IV fluids	severe	2
Respiratory compromise		
Tachypnea over 60/min with need for O_2 supplementation	mild/moderate	1
Need for C pap or mechanical ventilation	severe	2
Venous return		
Leg edema[a]	mild	1
Leg edema[b] with scrotal and/or sacral edema	severe	2
Renal		
Oliguria with output < 2ml/kg/hr	mild	1
Oliguria with signs of renal failure with rising BUN and creatinine	severe	2
Hepatic		
Thrombocytopenia/DIC platelet count < 50,000 cH	severe	2

[a]Thigh circumference > 75% ile [16].
[b]Thigh circumference > 90% ile [16].

or one, compared with 15 of 19 (79%) for the infants. What is striking, however, is the difference in the outcome between the two groups once a score of 2 or more is reached. None of the six neonates survived with such a score despite treatment, compared with four of six infants. Also, the neonate was more likely to develop serious compromise; half progressed to a score of 2 or more, whereas this occurred in only about a quarter (5 of 19) of the infants. The time to progression from diagnosis to treatment was a median of 5 days (1–34 days) and was not different between neonate and infant. In all but four patients, the score at the initiation of treatment was the same as the maximum; in the four patients it increased for a median of 3 days (2–8 days) after treatment commenced.

Treatment

The presenting signs and symptoms varied widely from asymptomatic with liver tumor nodules identified incidentally at laparotomy, to fetal distress due to hepatomegaly. No uniform treatment protocol was therefore used. Also, the time frame of this review is 50 years, during which time the available treatments and knowledge of their side effects have increased.

Most patients had exploratory laparotomy, with excision of the primary tumor, and examination and biopsy of the liver. A few patients had no laparotomy; instead, they had a percutaneous liver biopsy, skin biopsy, or bone marrow biopsy or aspirate to establish the diagnosis.

1944 to 1966. CT and other management varied according to the era reviewed. Ten patients were seen during this period including two neonates; five received no treatment, three received amino-an-fol or fluordeoxyuridine (FUDR), and two were irradiated. Four of the five untreated patients survived; the fifth (a neonate), was discharged home asymptomatic after removal of the primary tumor and was admitted to an outside hospital on day 31 in extremis, with a massively enlarged liver. (This patient accounts for the discrepancy in the total numbers of neonates, 13 scored at diagnosis, and only 12 for maximum symptomatology.)

1967 to 1994. Twenty-five patients were seen, of whom 14 were not treated; all 14 survived. Eight of 11 patients treated received RT with doses of from 300 to 1,000 cGy; and in three, this was combined with CT. Three were treated with CT alone. The agents used most often were cyclophosphamide (CPM) and vincristine (VCR) at a 50% reduced dose, and two later patients received etoposide and cisplatin. In four children, the attempt was made to decrease the abdominal pressure by incising the abdominal wall and allowing the liver to herniate. It was then covered with a Silastic or Gortex pouch [11]. This maneuver was successful in one patient; a second patient died of sepsis shortly postoperative, and in two patients it was ineffective in relieving the problems. Of the 11 patients treated since 1967, one of six neonates survive and four of five infants. The surviving neonate was asymptomatic and received treatment at 2 months postdiagnosis when she developed pleural plaques; these resolved after two 10-day courses of oral CPM.

Cause of Death

All the seven neonates who died had hepatomegaly at birth, and died from complications of the liver enlargement or its treatment (Table IV). One, mentioned above, was asymptomatic at diagnosis, and apparently developed progressive disease at home. The remaining six were treated; two died of hemoperitoneum, two of sepsis, one of organ failure due to IVC compression, and the one

TABLE III. Neonatal 4s Neuroblastoma: Neonate vs. Infant*

Score	Physiologic Score and Outcome: Neonate (4 weeks) alive/total	Infant (1–12 months) alive/total
At diagnosis		
0	5/7[a]	12/12
1	1/2	3/4[d]
2	0/2	1/2
3	—	—
4	—	—
5	0/1	—
6	0/1	1/1
Total	6/13	17/19 (no scores on 3 patients)
At treatment		
0	1/1[b]	2/2[c]
1	—	2/2[c]
2	—	—
3	0/3	—
4	0/1	1/1
5	0/1	1/2
6	0/1	1/1
Total	1/7	7/8
At maximum		
0	3/3	7/7
1	3/3	6/7[d]
2	0/2	1/1
3	—	—
4	—	1/1
5	0/2	—
6	0/2	2/3
Total	6/12	17/19

*The median time to progression from diagnosis to treatment was 5 days, and from treatment to maximum score was 3 days.
[a]One asymptomatic neonate died at 1 month at an outside hospital and no maximum score was available.
[b]One asymptomatic neonate received two courses of CPM at 2 months when she developed pleural plaques.
[c]Three of these four patients received amino-an-fol or FUDR in the 1950s, probably ineffective treatment for NBL.
[d]One asymptomatic infant died after progression to stage 4 at 2 years.

remaining died in the fourth month of liver and renal failure and a coagulopathy. Three of the 22 infants died, one of infection and DIC, one of radiation nephritis 5 months post-treatment similar to another patient reported by O'Malley et al. [12], and the third of widespread disease (like stage 4) at 2 years. The survival of 19 of 22 infants compared to six of 13 neonates is significant (Fisher Exact test $P = 0.02$) and only one of the three infant deaths were directly related to hepatomegaly. Autopsy findings were available in five of the six neonates who died. Two demonstrated widespread NBL in distant sites, often only in microscopic foci. Unusual loci of NBL included gonads, deep fat, pancreas, kidney, spleen, lungs, and thymus, none of which were life-threatening. Only one had extensive intra-abdominal spread.

A COMPARISON OF NEONATES WITH 4s AND NON-4s DISEASE

Six neonates with NBL stages 1 to 4 were found in a review of CHOP records from 1970 to 1994 (Table V). Most were cured by complete surgical excision. The only death attributable to NBL was a girl with a large mediastinal mass compressing the airways. It was partially resected and diagnosed as stage 3. She went on to have quadriparesis from high thoracic spinal cord compression and died of respiratory and neurologic deterioration. Thus, survival of neonatal NBL in stages other than 4s was five of six (83%), compared to six of 13 (46%) with 4s disease.

DISCUSSION

Patients with NBL stage 4s are at major risk when progressive hepatomegaly impairs vital functions. Our institutional management preference has been expectant observation of such patients so that those who will have early, spontaneous regression can avoid CT, and/or RT. Babies are especially vulnerable to CT-related immuno-

TABLE IV. Cause of Death in NBL 4s Babies*

Patient no.	Dx year	Age (wks)	Exc bx of "primary"	Adjunct Tx	Survival	Cause of death
5	1953	0	0	0	4 wks	massive hepatomegaly
10	1965	0	yes	RT	1 day	hemoperitoneum
12	1967	1	0	CT	8 days	sepsis and tumor
17	1975	1	0	RT/Pouch	8 wks	hemoperitoneum
31	1985	0	yes	RT	3.5 mo	tumor, IVH[a], liver failure
37	1992	0	0	RT/CT/Pouch	3 wks	IVC compression
38	1994	0	0	RT/CH	3 wks	sepsis, DIC
15	1972	12	0	CT/Pouch	2 wks	infection, tumor, DIC
6	1954	18	yes	RT	5 mos	radiation nephropathy, pulmonary edema
26	1980	30	0	0	37 mos	late recurrence

*See text for abbreviations used.
[a]Intraventricular hemorrhage.
Dx = Diagnosis
Exc bx = Excisional biopsy
Tx = Treatment

TABLE V. Neonates With NBL Stages 1 to 4, Compared With 4s (1970 to 1994)

NBL stage	Dead	Alive	Comments
1	0[a]	1	1 alive after local radiation for recurrence
2	0	2	2 alive after complete resection
3	1	1	1 died of respiratory and neurologic complications of unresectable mediastinal mass
			1 alive after complete resection large adrenal mass
4	0	1	1 alive after 2 courses 450 cGy to abdomen; 13 courses CPM, DTIC, VCR; resection of adrenal primary. Had skin, marrow, liver, ischial and femoral involvement
Total	1	5	5 of 6 = 83% survival
4s Total	7	6	6 of 13 = 46% survival

[a]Omitted are four neonates who were diagnosed NBL stage 1 as an incidental finding at autopsy, after dying for other reasons.

and myelosuppression, which can be fatal, and to RT-related growth disturbances. Oncogenesis is a problem after either CT or RT. This management preference was evident in the cases reviewed, so that CT or RT were given only to symptomatic patients, especially those with enlarging livers.

Published series have, however, noted that the youngest babies with NBL stage 4s have a worse prognosis than older infants, largely due to massive hepatomegaly. De Bernardi et al. [6] reported the NBL experience of the Italian Cooperative Group, with 76 patients from 1976 to 1991. They found a 68% survival rate in 30 NBL 4s babies diagnosed when less than 2 months old, and 90% survival in 46 of those diagnosed from 2 to 11 months of age. This difference in survival was statistically significant. They also conclude that "infants who were younger than 2 months of age and had massive abdominal disease were at high risk of dying of disease progression. No therapy was apparently effective in altering the course of disease in such patients." From 1976 to 1984, most of their infants less than 6 months old were treated with two cycles of Peptichemio (m-L-sarcholysin oligopeptide mixture). Since 1985, their group has recommended this agent for 6 to 11 month old infants with both stage 4s and 4, and avoiding anti-tumor treatment in infants less than 6 months old.

Suarez et al. [8] reported the Institut Gustave Roussy protocol for NBL 4s in 34 patients seen from 1982 to 1987 and given treatment only if presenting with life-threatening symptoms or if progressive disease was observed. They record 73% survival for 11 patients less than 1 month old at diagnosis and 83% for 23 patients 1 to 9 months old at diagnosis. The difference in survival was not statistically significant.

Wilson et al. [14] describe 18 NBL 4s patients seen at The Toronto Hospital for Sick Children in the interval 1971 to 1988. They report survival of 3/7 patients (43%) less than 6 weeks old at diagnosis, and 6 of 11 patients (55%) 6 weeks to 6 months old. Stephenson et al. [5] also found that patients under 6 weeks of age at diagnosis and without skin involvement were "high risk" (32% survival), while "low risk" patients had 93% survival. Stratifying their patients by age at presentation without regard for skin involvement yields 54% survival for age 6 weeks or younger, and 84% survival for 7 weeks to 12 months. Their review of 137 patients includes cases from the Walter Reed Army Medical Center, the Armed Forces Institute of Pathology, and multiple published reports. Nickerson et al. [4] surveyed The Children's Cancer Study Group institutions for the period 1972 to 1979 for NBL stage 4 and 4s: they reported 75% survival in 12 4s patients less than 2 months at diagnosis, and 97% survival in 32 patients 3 to 12 months at diagnosis. Many of their patients had been described previously. They suggest that "high risk stage 4s patients less than 2 months old at diagnosis may need treatment similar to stage 4 disease." It is thus noteworthy that surveys encompassing many years with many treatment modalities and at many different institutions yields a common theme; viz., the vulnerability of the younger compared with older infants with 4s NBL. Although the definition of "young" age varies, the reported range of survival is 43% to 75%, and for "older" infants, it is 55% to 97%. Our results of 46% and 86% fall within these ranges.

Our study indicates that the neonate is least resilient in the face of physiologic compromise. We therefore identified the organ systems that seem most at risk [9,10], and developed a semiquantitative scoring system that focuses on the early signs and symptoms of organ stress caused by the hepatomegaly characteristic of 4s disease. These include digestive, respiratory, vascular and renal complications, and disseminated intravascular coagulation. Because of the time period covered by this review, not all of the measurements included in Table II were available. They have been used in the suggested scoring system to provide more objective criteria for the clinician of today. Our data suggest that infants who have no appreciable symptoms or signs of

physiologic compromise at diagnosis need not be treated. They should be observed carefully for evidence of organ dysfunction, using Table II as a guide. A score of one in a neonate, however, calls for treatment in order to slow or reverse tumor growth. Although these babies are notoriously resistant to treatment [6], the results shown in Table III indicate (but do not prove) that intervention can be successful in infants. It is hoped that neonates would also be amenable to timely treatment. Particular attention should be paid to GI symptoms because intervention in the neonate with GI symptoms alone appears to have a better prognosis than waiting until a second physiologic system is involved. Older infants with 4s appear less vulnerable than neonates, and may be observed without intervention until a total score of 2 is reached, e.g., mild symptoms in 2 systems. A score of more than 2 suggests the need for urgent, aggressive therapy. Another index we have found useful and not previously mentioned, is periodic measurement of the maximum abdominal girth. An increase of >1 cm in 48 hours in a neonate is a warning signal, and calls for especially careful surveillance, as in the case report above. Treatment may include local radiation to the liver using techniques that spare the kidneys and vertebral column [13], CT adjusted for age, and sometimes creating an artificial ventral hernia in extreme cases [11].

We attempted to validate the scoring system by a retrospective analysis. The patients and the scores assigned to them were reviewed retrospectively to see whether their management would have been different had the present scoring system been used. All but one of the 22 untreated patients would not have been treated, and all 21 fared well. The 22nd child would have been treated. He was a neonate who was found to have hepatomegaly in 1953, and was sent home without treatment presumably because he was thought to have metastatic neuroblastoma for which no effective therapy was known. He died of "cardio-pulmonary arrest" one month later at another hospital. Two untreated neonates developed feeding problems 6 weeks after diagnosis for a score of one, which in babies >4 weeks old would not call for therapy today. They both are alive and well. Three treated babies, two neonates and one infant, had scores retrospectively assigned such that they would have had therapy initiated earlier. The two neonates died; the third child survives. Lastly, three treated infants with scores of one would not be treated today. All three are alive and free of disease. This retrospective analysis demonstrates that the scoring system appears to predict the clinical evolution of 4s disease in these age groups.

This was a retrospective review of the experience at a single institution, and there is a potential sample bias of cases with poor outcome which would appear in the pathology and tumor registry records. Patients were not treated according to a uniform protocol, but on the judgment of the physician at the time. Retrospective scoring of symptoms is imperfect. It was not possible for three of the 35 patients, and not all clinical details were available in the charts of all children for the entire clinical course. Furthermore, some more objective measures of distress such as oximeter readings were not even in use throughout the time period covered and thus could not be used for these analyses.

Some authors have stated that the concept of stage 4s disease is obsolete [14]. We do not agree, anymore than staging, in general, is obsolete. We do agree that better outcome predictors such as specific biologic markers could be helpful in identifying those neonates and infants with a poor prognosis [15]. However, they would not influence initial management of these children who manifest increasing physiologic distress, and for whom clinical criteria such as those proposed here are more practical and immediate.

We summarize and conclude that careful attention to the clinical course of the baby with NBL 4s is essential. We offer a guide to intervention (a scoring system), based on increasing physiological distress in organs adjacent to the liver, and secondary to its enlargement. This is the major threat to life. The present review has modified our approach to therapy so that we now treat neonates at the first sign of physiologic compromise (a score of one), whereas older babies can be watched until more severe signs become apparent (a score of 2 or more).

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